Editorial

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Granulosa cell tumor of the ovary: time to launch a new prospective trial

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It is not easy to define the clinical course or establish a consensus in the management of a disease with a relatively low incidence such as granulosa cell tumor (GCT). They represent less than 2% of all ovarian tumors, but account for 6% of all ovarian malignancies [1]. GCTs generally have indolent growth however the potential for malignancy makes them clinically significant. Although the late recurrence might be considered a favorable characteristic, their unpredictable behavior, particularly for the adult type, can complicate management. Owing to the relative infrequency with which GCTs occur, many studies regarding the outcome and treatment are small-sized and retrospective, and therefore difficult to implement adequately powered clinical trials; however, this does not imply that small-scaled trials have no value at all.

In this issue of Journal of Gynecologic Oncology, Lee et al. [2] reported a multicenter retrospective observational data of 113 women with GCTs. Despite its retrospective nature; this is the first multicenter observational study currently available in Korea. It is worthy of attention because the authors put effort to recruit patient data from 5 different institutions in an attempt to provide helpful clinical insight of the disease. The authors were keen to investigate both adult and juvenile types and also included endometrial assessment data. Endometrial cancer occurs in association with granulosa cell tumors in at least 5% of cases, and 25% to 50% are reported to be associated with endometrial hyperplasia due to the stimulation of endometrium by unopposed estrogen production [3,4]. In this study, endometrial evaluation was available in 68 patients (66.7%). Among them, 18 patients (17.6%) had endometrial abnormalities including simple and complex hyperplasia, and one patient had expired due to endometrial cancer recurrence. This finding flags up the risk of endometrial abnormalities related to this disease and stresses the importance of ruling out concomitant endometrial pathology.

Another acknowledgeable finding presented in this study is the follow-up data of subsequent pregnancies. Fertility sparing surgery with unilateral salpingo-oophorectomy can be a reasonable approach for early stage GCT patients wishing to preserve their fertility. However, publications addressing the subsequent pregnancy outcomes after a conservative surgery are scarce [5,6]. This may be mainly due to the limited number of patients seen in any single institution over a short period. In a population-based study by Zanagnolo et al. [6], a conservative surgical treatment was performed in 23% of early-stage tumors, none of them recurred, and five of 11 patients became pregnant after treatment. Although detailed information on the pregnancy outcome such as gestational weeks and mode of delivery are lacking in this study by Lee et al, it corresponds to the previous reports with favorable fertility outcome; 36 patients (35.5%) underwent fertility-sparing surgery and not only there was an insignificant difference in recurrence or survival compared with those who had received radical surgery, 8 patients became pregnant. Nonetheless, there are some clinicians that believe the primary treatment as the main determinant of relapse and survival rates. This reinforces the necessity for initial comprehensive surgical exploration and accurate staging [7]. Three patients in this study who received only cystectomy are of special concern

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because despite the controversy and lack of standardization of the initial surgical procedure, the fact that GCTs are still tumors of low grade malignancy should not be overlooked. It is important to remember that performing a more conservative surgery is under the condition of careful staging which reveals that the disease has not extended outside the involved ovary and that a concomitant uterine cancer has been excluded.

Stage was the only prognostic factor for predicting recurrence in this study which finding corresponds well with the previous reports [5,8]. However, due to the rarity of the disease, tumor-dissemination patterns and prognostic factors are not well defined and are mostly based on retrospective data. Prognostic factors are important because the management of advanced or recurrent GCTs may not be as simple and favorable as early stage diseases. According to a study by Fotopoulou et al. [4], the tumor dissemination patterns differed significantly between primary and recurrent patients, having significantly higher rates of diffuse peritoneal involvement and extraovarian tumor involvement of the middle and upper abdomen in the recurrent cases. Not surprisingly, only about 85% of the relapsed patients could be operated without residual lesions compared to nearly 100% in all primary patients [4]. Again, the value of postoperative adjuvant therapy for high-risk patients has not been investigated by prospective randomized trials, which are difficult to perform because of the rarity of this tumor.

Likewise, the rarity of a disease brings some special problems where there are simply not enough patients to produce the quantity of evidence that we might generally wish to see. Nevertheless, it is our task as clinicians to present the best evidence we can, when gold standard evidence is not obtainable. Although small-sized and retrospective, there are considerable numbers of independent studies regarding GCTs. They may have differences, but they are also sufficiently similar that combining their results can lead to a conclusion that is clinically interpretable and useful. Therefore, now might be the time for a pre-planned meta-analyses and more collaboration to launch prospective studies for a standardized treatment protocol of GCTs. What aspects should be considered to start a successful prospective trial? The first and the most important point will be patient recruitment. Not only rare in incidence, the interval from initial treatment to recurrence is long, which may produce a problem in long-term patient follow-up. One-third of recurrences present after more than five years after initial treatment and the longest documented time for recurrence in the literature was 37 years [9]. Therefore, adequate information of the disease including the low incidence of recurrence should be provided through patient counseling for a durable trial. Secondly, in return for the altruism and trust from the volunteers that make clinical research possible, the researchers have an obligation to conduct an ethical study and report it honestly. A disciplined education regarding study ethics and strict protocols by the Institutional Review Board should be encouraged. When the patients are adequately guided through the evidence to make proper informed decisions then will the novel therapeutics and moral outcomes begin to unfold from the well-designed future trials.

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